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(54) Title: ISOSORBIDE ASPIRINATE ESTERS

(57) Abstract

Isosorbide 2–aspirinate, Isosorbide 5–aspirinate, and especially Isosorbide 2,5–diaspirinate compounds are stable compounds which may be administered to achieve anti–platelet activity and/or other aspirin type activities. The compounds may be used with other therapeutic agents to achieve a combined therapeutic effect. In particular, the compounds may be formulated in a capsule with a therapeutic oil, especially Cod Liver Oil.

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ISOSORBIDE ASPIRINATE ESTERS

The invention relates to aspirinate compounds.

Aspirin, which has been available for about 100 years, possesses analgesic, anti-inflammatory and antipyretic properties. This compound has also been shown to be effective in cardiovascular disease and this action dependent upon its effects on platelet function. Aspirin can improve the mortality figures associated with acute myocardial infarction and reduces the risk of this in patients with unstable angina by between 30 and 50%. It is used to prevent re-occurrence in those patients after recovery from myocardial infarction. It is also likely to be of benefit to individuals suffering from stable angina since it reduces the risk of myocardial infarction in apparently healthy, middle-aged men. Aspirin is used to reduce the likelihood of stroke in patients with transient cerebral ischaemic attacks. It also lowers the risk of thromboembolism in patients with atrial fibrillation and following valve replacement.

Aspirin reduces platelet aggregation by irreversibly inhibiting fatty acid cyclo-oxygenase, a precursor in the biosynthesis of prostaglandins and thromboxanes. This occurs by acetylation of a serine residue and thus prevents access of arachidonic acid to the active site by steric hindrance. Thromboxane A2 is the main cyclo-oxygenase product of activated platelets and is proaggregatory and a vasoconstrictor. Therefore, aspirin exerts its antithrombotic action by preventing thromboxane A2 biosynthesis. Although other non-steroidal anti-inflammatory drugs also possess this effect they are much less effective because, unlike aspirin, they reversibly inhibit the enzyme.

Although the use of oral aspirin has been used for these conditions, there are a number of disadvantages associated with this treatment. The compound has been associated with various gastrointestinal side effects the most severe of which can be gastric bleeding occurring in about 70% of patients taking oral aspirin.

Furthermore, the drug is extensively hydrolysed by first-pass metabolism and possesses a half life of about 15 minutes. Salicylic acid, a metabolite of aspirin, has relatively little anti-platelet activity.

Aspirin is also relatively unstable, especially in formulations with other therapeutically active substances.

There is therefore a need to provide stable and viable compounds with aspirin-like activity but which will not have the disadvantages associated with Aspirin. This invention is directed towards providing such compounds.

According to the invention there is provided an isosorbide aspirinate compound.

In particular, the invention provides the compounds Isosorbide-2-aspirinate, Isosorbide-5-aspirinate and, especially Isosorbide-2, 5-diaspirinate.

The invention also provides a pharmaceutical composition comprising a compound of the invention which may be adapted for oral administration as a capsule or tablet or for percutaneous administration, for example in the form of a transdermal patch. The composition may also be in the form of a suppository.

The invention also provides the use of the compound to achieve anti-platelet activity and/or other aspirin type activities such as anti-pyretic and/or anti-inflammatory activity.

In a particularly preferred embodiment of the invention the composition includes another pharmaceutical entity, especially a therapeutic oil, typically a fish oil such as cod liver oil, or a vegetable oil such as evening primrose oil. In this case the composition maybe in the form of a capsule having a retaining shell containing a filling including the active ingredients. The filling may include a suspending agent such as one selected from one or more of colloidal silicon dioxide, hydrogenated

vegetable oils (optionally in combination with beeswax), high melting point partial glycerides, and/or lecithins. The filling may also include an antioxidant such as one selected from one or more of D-alpha tocopherol, D-alpha tocopherol acetate, mixed tocopherols and ascorbic acid. The shell may be a gelatin shell.

The invention also provides a process for preparing a compound of the invention.

The invention will be more clearly understood from the following description thereof given by way of example only.

Example 1 - Isosorbide-2, 5-Diaspirinate

The reaction scheme is given in appendix 1.

The title compound was prepared in satisfactory yield without the use of chromatography by stirring a mixture of isosorbide, triethylamine and acetylsalicyloyl chloride in toluene for a period of 24-36 hours. The reaction mixture was then washed with 2M HCl, to remove some of the side products and the excess base. The removal of any unreacted aspirin was achieved by washing with a saturated sodium bicarbonate solution. This afforded a material whose major component was the title diaspirinate ester by Thin Layer Chromatography. This ester was crystallised by dissolving it in ethanol. Much of the colour was removed following the first crystallisation. A second crystallisation yielded a higher purity material. A third or fourth recrystallisation was required to achieve a purity of greater than 99.8%. A sample procedure is given below. The reaction was performed under anhydrous conditions so that only a small excess of the acid chloride was required.

Acetylsalicyloyl chloride* (6.3 g, 30 mmol, 2.2 eq.) was suspended in toluene (50 cm^3) and triethylamine (5 cm^3) was added. The mixture was cooled to 0°C and light excluded. Maintaining the temperature, isosorbide (2.0 g, 13.7 mmol)

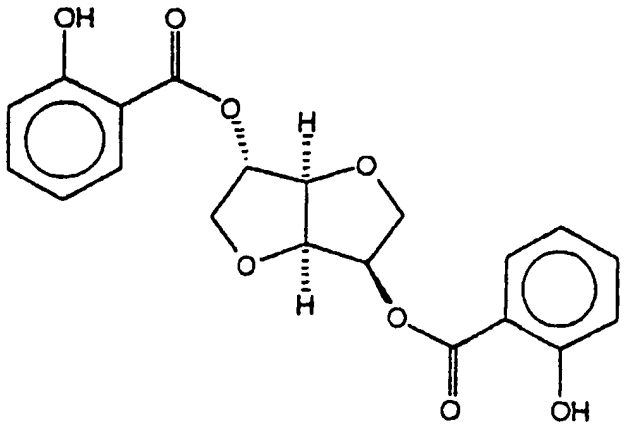
was added to the stirring solution. When the addition was complete the resulting mixture was allowed to reach room temperature with vigorous stirring. The reaction was monitored by TLC† (following a mini-work up). After 36 hours the reaction was pale orange. The mixture was washed thoroughly with 2M HCl (2 x 50 cm^3) and saturated aqueous sodium bicarbonate (50 cm^3) and water (50 cm^3), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* yielding an orange solid. This contained the title compound as one major component by HPLC. The residue was crystallised from ethanol. A second crystallisation from ethanol yielded the title compound in greater than 99.85 purity.

* The acetylsalicyloyl chloride used was the 96% pure grade as supplied by Fluka.

† Thin layer Chromatography was performed on Kieselgel 254 (Al backed plates) Rf = 0.64 using ethyl acetate:petroleum spirits (1:1) as the mobile phase. Visualisation was done using U.V. at 254 nm (the title compound is inactive at 366nm) and iodine stain.

Compound name: isosorbide-2, 5-diaspirinate or 2, 5-di (2-acetoxybenzoyl) – iso-sorbide, or 2,5- diacetylsalicyloxy-1, 4:3, 6-dianhydro-D-glucitol

Structural formula of compound:



Empirical formula	$C_{24}H_{22}O_{10}$
Molecular mass:	470.4gmol^{-1}
Appearance:	colourless crystalline solid
Melting Point:	110.5-111.5°C at 1.5°C/min

Differential Scanning Calorimetry:

Endothermic Effect: 109-118°C (measured at 10.0°C/min).

Optical rotation:

Specific Rotation: $[\alpha]_D$ = +42.0 (24.5°C, 1.0% in Dichloromethane) (recorded on an optical activity LTD AA10 Automatic Polarimeter, using a 2dm sample tube).

Thin layer chromatography

R_f Value: 0.64 on Kieselgel A1 backed plates 254nm (mobile phase-ethyl acetate/petroleum spirits bp 40-60°C, 1:1)

Elemental analysis:

Required:	C%; H%.	61.28%; 4.71%
Found:	C%; H%.	61.46%; 4.72%

Mass spectrum:

FAB+ (m/z): 471.1271 (MH^+)

Spectroscopic data:

^1H NMR:

(300 MHz $CDCl_3$)

δ 2.34 (3H, s, OCOMe); 2.36 (3H, s, OCOMe); 3.93-4.13 (4H, m, IS1-(α + β) H, IS6 – (α+β)H); 4.59 (1H, d, *J*4.8 Hz, IS3-H); 4.98 (1H, m, IS4-H); 5.35-5.46 (2H, m, IS2-H, IS5-H); 7.07-7.14 (2H, m, ArH-3), 7.27-7.37 (2H, m, ArH-5); 7.53-7.62 (2H, m ArH-4); 7.95-8.11 (2H, m, ArH-6).

^{13}C NMR:

(75.5 MHz, $CDCL_3$):

δ 20.85 (OCOMe); 0.94 (OCOMe); 70.63 (ISC-6); 73.06 (ISC-1); 74.43 (ISC-2); 78.38 (ISC-5); 80.96 (ISC-4); 86.00 (ISC-3); 122.54, 122.58 (ArC-1); 123.76, 123.90 (ArC-3); 126.00, 126.06 (ArC-5); 131.77, 131.96 (ArC-4); 134.18, 134.26 (ArC-6); 150.59, 150.69 (ArC-2); 163.50, 163.66 (ArOCOMe), 169.57, 169.61 (ArC(O)OR).

IR:

ν(C=O) 1767.2, 1727.3, 1706 cm^{-1}

UV:

λMax: 228.1 nm, 276.5 nm

Impurity Profile:

Analysis by HPLC indicated >99.8% purity. The compound is homogeneous by thin layer chromatography.

Solubility Studies:

Solvent	Cold	Hot
Water	insoluble	very sparingly
Methanol	sparingly	soluble
Ethanol	sparingly	soluble
Diethylether	sparingly	soluble
Dichloromethane	soluble	soluble
Toluene	soluble	soluble
Ethyl acetate	soluble	soluble

Stability Studies

The stability of the solid compound (isosorbide – 2, 5 – diaspirinate) under accelerated conditions of 40°C over a 12 week period was studied. At time O approximately 1.5 g of the solid compound (100% pure by HPLC) was distributed between six sealed sample bottles. A heated sample (≈ 0.020 g) was weighed into a 10 ml volumetric flask, acetonitrile (4 ml) added, and the volume was brought up to 10 ml with Milli – Q (trade mark) purified water. 1 ml of this solution was transferred to a clean dry class A volumetric flask and 4 ml of acetonitrile were added. The volume was made up to 10 ml with aqueous mobile phase. Each sample was filtered, using a disposable syringe with an Acrodisc (trade mark) filter connected, into a sampling vial for analysis using HPLC.

Samples were tested every 2 weeks and the concentrations in mg/ml of the compound and any breakdown components at 40°C were determined. No breakdown components were detected and the concentration of the compound was maintained as follows.

Time (week)	Concentration of Compound (μg/ml)
2	198
4	199
6	198
8	196
10	198
12	200

From these results it can be concluded that there is no degradation of the compound at 40°C after three months.

The stability of the compound (isosorbide – 2, 5 – diaspirinate) (ISDasp) in cod liver oil (CLO – BP) in the presence of water and/or glycerol was also determined. The stability of the compound compared to that of aspirin under the same conditions was also determined.

The following samples were prepared:

Samples A – E were mixtures of the ISDasp in CLO-BP with variable water/glycerol concentrations (0.208 mmol of aspirinate).

Samples F-J were mixtures of aspirin in CLO-BP with similar concentrations of water/glycerol to that for the ISDasp samples (0.208 mmol aspirin).

Each set was prepared six times for studying in weeks 0, 1, 2, 4, 8 and 12.

A: 48.96 mg ISDasp, 500 mg CLO BP

B: 48.96 mg ISDasp, 500 mg CLO BP, 2.5% water

C: 48.96 mg ISDasp, 500 mg CLO BP, 5.0% water

D: 48.96 mg ISDasp, 500 mg CLO BP, 5.0% glycerol

E: 48.96 mg ISDasp, 500 mg CLO BP, 5.0% water, 5.0% glycerol

F: 37.50 mg Asp, 500 mg CLO BP

G: 37.50 mg Asp, 500 mg CLO BP, 2.5% water

H: 37.50 mg Asp, 500 mg CLO BP, 5.0% water

I: 37.50 mg Asp, 500 mg CLO BP, 5.0% glycerol

J: 37.50 mg Asp, 500 mg CLO BP, 5.0% water, 5.0% glycerol

Extraction Procedure for ISDasp from the Cod Liver Oil Mixture

To the vial containing the Cod Liver Oil (CLO) sample was added 1.2 ml of acetonitrile. The mixture was gently shaken by repeatedly inverting the sealed vial for 1 minute. The sample was sonicated for a further three minutes. Hexane (2 ml) was added and the sealed vial shaken gently for another minute. The layers were allowed to settle out (approximately 3-5 mins). The upper hexane/CLO layer was siphoned off. A 120 ml sample of the remaining acetonitrile layer was added to a class A 10 ml volumetric flask and 5 ml acetonitrile, 2 ml aqueous mobile phase added and the volume made up to 10 ml with milli-Q water. A sample of the solution was filtered using a disposable syringe and Gelman FP vericel membrane filter to yield a clear solution for analysis.

Extraction Procedure for Aspirin from the Cod Liver Oil Mixture

To the vial containing the Cod Liver Oil (CLO) sample was added 0.5 ml of acetonitrile. The mixture was gently shaken by repeatedly inverting the sealed vial for 1 min. The sample was sonicated for a further three minutes. Hexane (1.5 ml) and milli-Q water (1 ml) were added and the sealed vial shaken gently for 1 min. The layers were allowed to settle out (approx. 3-5 mins). The upper hexane/CLO layer was siphoned off. A 120 ml sample of the remaining aqueous layer was added to a class A 10 ml volumetric flask and 5 ml acetonitrile, 2 ml aqueous mobile phase added and the volume made up to 10 ml with milli-Q water. A sample of this slightly cloudy mixture was filtered using a disposable syringe and Gelman FP Vericel membrane filter to give a clear solution.

Extraction analysis was by chromatography as follows:

Isosorbide diaspirinate; ISDasp samples were analysed using a similar chromatographic procedure to that used in the solid stability study; acetonitrile: buffer 40:60, PDA detection with chromatogram extraction at 230 nm.

Aspirin; Aspirin samples were analysed using a mobile phase of acetonitrile: buffer 15.85, PDA detection with chromatogram extraction at 230 nm.

Stability Study

Samples of isosorbide diaspirinate and aspirin placed on stability at 26°C were analysed following 15 weeks using the extraction procedure outlined above.

Table 1; Analysis of CLO/aspirin mixtures following 15 weeks at 26°C

Sample	Aspirin			Salicylic acid		
	a.n.%	conc	recovery*	a.n.%	conc	Amount %
F	98.4	262ug	87%	1.6	3.9ug	1.50%
G	98.1	252ug	84%	1.7	4.0ug	1.60%
H	97.6	260ug	87%	2.2	5.3ug	2.00%
I	98.1	220ug	74%	1.7	3.9ug	1.78%
J	96.1	243ug	81%	3.6	8.5ug	3.50%

concentration determined by external standard (100 ug/ml asp. and sal.)

*Based on a theoretical maximum concentration following dilution of 300ug/ml.

a.n. ⇒ % area by area normalisation of chromatograms of samples following extraction and dilution.

Amount % salicylic acid is calculated with respect to the weight of aspirin.

Table 2: Analysis of CLO/diaspirinate mixtures following 15 weeks at 26°C

Sample	ISDasp			Total Salicylate		
	a.n.%	Conc	recovery*	a.n.%	conc	Amount %
A	99.20	375ug	77%	n.d.	-	-
B	98.10	411ug	84%	0.02	0.1ug	0.04
C	89.60	405ug	83%	1.30	0.58ug	1.30
D	99.70	399ug	82%	0.03	0.15ug	0.04
E	96.09	409ug	84%	0.03	0.15ug	0.04

- concentrations determined by external standard (100ug/ml, diasp and is-2-asp-5sal)

*Based on a theoretical maximum concentration of 490 ug/ml following dilution.
Amount % salicylate calculated with respect to Diaspirinate
a.n. ⇒ % area by area normalisation of chromatograms of samples following extraction and dilution.

The compounds of the invention have potential therapeutic use by virtue of the inclusion of an aspirin moiety as an anti-platelet agent and/or to achieve other aspirin type activities such as anti-pyretic and/or anti-inflammatory activity.

Isosorbide diaspirinate administered at 2 mg/kg in single oral doses to adult beagle dogs have shown that the compound has aspirin – like activity as measured by inhibition of arachidonic acid – induced platelet aggregation (inhibition of cyclooxygenase activity), and inhibition of ex vivo production of thromboxane B_2.

The compounds of the invention may be formulated in any suitable pharmaceutical compositions using conventional excipients/vehicles. For example, the composition may be presented in a form for oral administration (typically in a tablet or capsule form), in a form for percutaneous administration (typically in the form of a transdermal patch), or in a suppository formulation.

A suppository formulation may in some cases be preferred as a route of administration because it avoid absorption in the gut. One typical suppository formulation is as follows. Micronised isosorbide-diaspirinate (6g) was added to 5g of a suppository base such as Novata E (trade mark of Henkle) which was previously gently melted over a steam bath at 80 to 90°C. The mixture was allowed to cool slightly and then poured with vigorous stirring into 10 x 1 g suppository moulds.

The compounds of the invention may be administered at a suitable dose to achieve the desired therapeutic benefit. In an oral dose to achieve anti-platelet activity an amount of the compound equivalent to 50 to 150, preferably 100, mg of aspirin per day may be administered. To achieve an analgesic effect a higher dose would typically be administered. In a suppository formulation the dosage would also typically be higher.

The results above show that isosorbide diaspirinate is substantially more stable than aspirin in the test conditions.

The compounds may be formulated with cod liver oil to achieve a combined therapeutic effect. The compounds may also be combined with another fish oil or a therapeutic oil in general such as a vegetable oil, for example evening primrose oil.

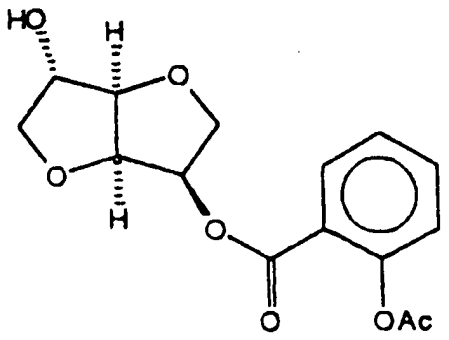
The formulation may be in the form of a gelatine capsule with a filling including the active ingredients. The filling may include an antioxidant and/or a suspending agent.

The suspending agent may be selected from one or more of colloidal silicon dioxide, hydrogenated vegetable oils (optionally in combination with beeswax), high melting point partial glycerides, and/or lecithins.

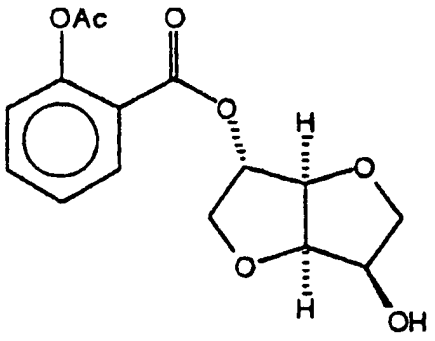
The antioxidant may be selected from one or more of D-alpha tocopherol acetate, mixed tocopherols and ascorbic acid.

More generally, it is anticipated that the compound may be combined with other therapeutic agents to achieve a combined therapeutic effect.

The invention also provides the following compounds which may be formulated and used as described above in relation to the compound of example 1.



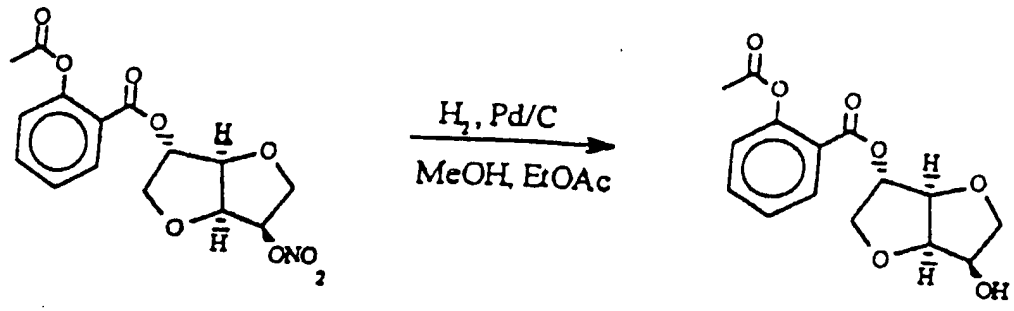
Isosorbide-5-aspirinate (IS-5-A)



Isosorbide-2-aspirinate (IS-2-A)

Example 2:

Preparation of *Isosorbide-2-aspirinate* [2]



1 2

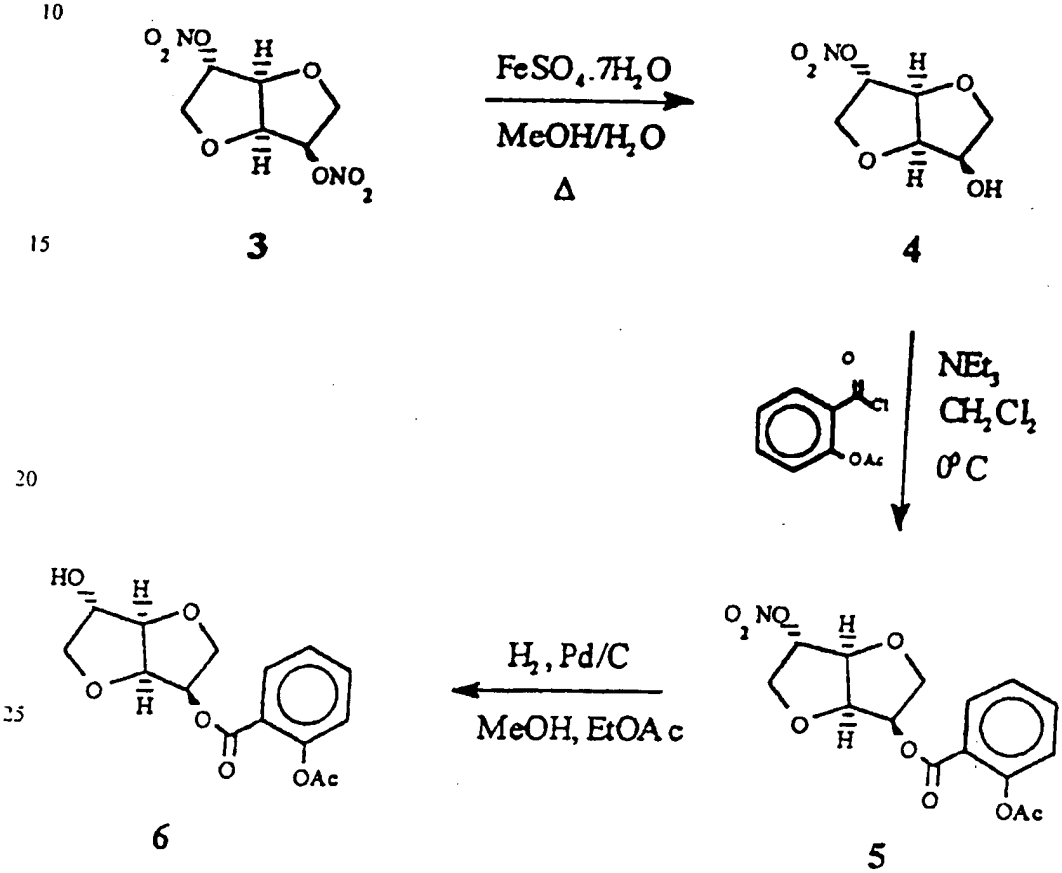
Isosorbide mononitrate aspirinate (3.5g 10mmol), in a mixture of methanol and ethyl acetate (60 ml, 1:1), was stirred for 24 hours over palladium on charcoal under an atmosphere of hydrogen. The reaction was monitored by TLC, and showed the formation of a single product. The reaction mixture was filtered and concentrated under reduced pressure, and flash chromatography using chloroform/ether (4:1) as the mobile phase gave the aspirinate 2 as a colourless oil, m.p. 59-61°C.

δ_H (300MHz; $CDCl_3$): 2.34 (3H, s, $OCOCH_3$), 2.71 (1H, d, J 9Hz, OH), 3.59 (1H, dd, J 9.4 and 5.9Hz, IS6α-H), 3.90 (1H, dd, J 9.6 and 6.2Hz, IS6β-H), 4.06 (1H, dd, J 10.7 and 3.5Hz, ISIβ-H), 4.14 (1H, d, J 10.7Hz, IS1α-H), 4.31 (1H, m, IS5-H), 4.56 (1H, d, J 4.4Hz, IS3-H), 4.66 (1H, m, IS4-H), 5.42 (1H, d, J 3.1Hz, IS2-H), 7.09 (1H, m, ArH-3), 7.31 (1H, m, ArH-5), 7.57 (1H, m, ArH-4), 7.99 (1H, m ArH-6).

δ_C (75.5MHz; $CDCl_3$); 20.8 ($OCO\underline{C}H_3$), 72.2 (ISC-5), 73.3 and 73.5 (ISC-1 and ISC-6), 78.8 (ISC-2), 81.9 (ISC-4), 85.4 (ISC-3), 122.6 (ArC-1), 123.8, 126.0, 131.7 and 134.3 (aromatic methine), 150.6 (ArC-2), 163.4 and 169.6 ($ArO\underline{C}(O)Me$ and $Ar\underline{C}(O)OR$).

Example 3:

Preparation of *Isosorbide-5-aspirinate* [6]



3 4 5 6

Isosorbide-2 mononitrate 4:

Isosorbide-2, 5-dinitrate 3 (3.95g, 16.7 mmol) was dissolved in a mixture of methanol and water (100ml, 4:1), and ferrous sulphate ($FeSO_4.H_2O$, 15.0g, 54.0mmol) was added at room temperature. The mixture was heated to reflux temperature for 4h before removing the methanol under reduced pressure. The product was extracted into dichloromethane (3x50ml), washed with saturated aqueous sodium bicarbonate, and was dried over magnesium sulphate. The solvents were removed to yield a pale yellow oil. Flash column chromatography, using dichloromethane:ethyl acetate:pet. ether (1:1:1) as the mobile phase gave isosorbide-2-mononitrate 4 as a colourless oil (1.51g, 47%).

δ_H (300MHz; $CDCl_3$): 2.73 (1H, d, J 6.6Hz, OH), 3.60 (1H, dd, J 9.4 and 5.7Hz, IS6α-H), 3.88 (1H, dd, J 9.4 and 5.7 Hz, IS6β-H), 4.05-4.17 (2H, m $IS1H_2$[α + β]), 4.30 (1H, m, IS5-H), 4.54 (1H, d, J 4.6Hz, IS3-H), 4.62 (1H, m, IS4-H), 5.36-5.40 (1H, m IS2-H).

δ_C (75.5MHz; $CDCl_3$): 71.60 and 73.40 (ISC-1 and ISC-6), 72.03 (ISC-5), 82.05 (ISC-4), 83.90 (ISC-2), 86.27 (ISC-3).

Isosorbide-5-aspirinate-2-mononitrate 5:

Isosorbide-2-mononitrate 4 (1.38g, 7.2mmol) was dissolved in anhydrous dichloromethane (50ml) and triethylamine (2.19g, 21.6mmol) was added. The mixture was cooled to 0°C for the introduction of acetylsalicyloyl chloride (1.43g, 7.2mmol). The mixture was stirred for 16h at room temperature before washing with 2.OM HCl, water and saturated aqueous sodium bicarbonate. The organic phases were dried over magnesium sulphate and were concentrated under vacuum to give a yellow oil. Flash column chromatography, using ethyl acetate:dichloromethane:pet ether (1:1:3) as the eluant gave the desired product,

isosorbide-5-aspirinate-2-mononitrate 5, as a pale yellow oil (1.68g, 66%). This was crystallised from ethanol to yield colourless crystals; m.p. 88-90°C.

δ_H (300MHz; $CDCl_3$): 2.36 (3H, s, $OCOCH_3$), 3.95-4.16 (4H, m, IS1H_2[α+β]) and IS6H_2[α+β]), 4.60 (1H, d, J 5.1Hz, IS3H), 4.94 (1H, m IS4-H), 5.36-5.39 (2H, m, IS2-H and IS5-H), 7.12 (1H, m, ArH-3), 7.33 (1H, m, ArH-5), 7.59 (1H, m, ArH-4), 8.05 (1H, m, ArH-6).

δ_C (75.5MHz; $CDCl_3$): 20.94 ($OCO\underline{C}H_3$), 70.85 and 71.44 (ISC-1 and ISC-6), 74.01 (ISC-5), 81 09 (ISC-4), 84.40 (ISC-2), 85.91 (ISC-3), 122.40 (ArC-1), 123.93, 126.08, 131.84 and 134.29 (aromatic methine), 150.67 (ArC-2), 163.52 and 169.55 (Ar$\underline{C}$(O)OR and ArO$\underline{C}$OMe).

m/z (FAB) 354.08 $(M+1)^+$

Isosorbide-5-aspirinate 6:

Isosorbide-5-aspirinate-2-mononitrate 5 (0.16g, 0.45mmol) was dissolved in a mixture of ethyl acetate and anhydrous methanol (20ml, 1:1), and a catalytic amount of palladium on charcoal was added. The mixture was stirred under an atmosphere of hydrogen for 4h. TLC indicated the formation of two products: the desired isosorbide-5-aspirinate 6, and its salicylate. The reaction mixture was filtered and concentrated under vacuum. Flash column chromatography, using

dichloromethane/ethyl acetate/pet. ether (1:1:1) as the eluant, was carried out on the crude product, yielding the aspirinate 6 as a colourless oil (0.11g, 79%).

δ_H (300MHz; $CDCl_3$): 2.35 (3H, s, $OCOCH_3$), 3.86-3.98 (4H, m, IS1H_2[α+β] and IS6H_2[α+β], 4.32 (1H, br, s, IS2-H), 4.41 (1H, d, J 4.6Hz, IS3-H), 4.92 (1H, m, IS4-H), 5.32 (1H, m, IS5-H), 7.10 (1H, m, ArH-3), 7.32 (1H, m, ArH-5), 7.57 (1H, m, ArH-4), 8.05 (1H, m, ArH-6).

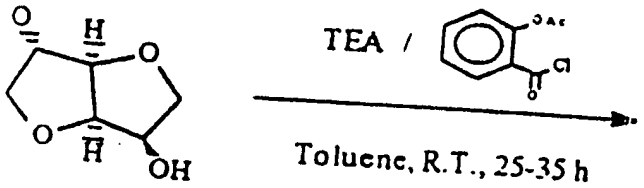
δ_C(75.5MHz; $CDCl_3$): 20.83($OCO\underline{C}H_3$), 70.31 and 75.46 (ISC-1 and ISC-6), 74.60 (ISC-5), 76.11 (ISC-2), 80.45 (ISC-4), 88.32 (ISC-3), 122.74 (ArC-1), 123.81, 125.93, 131.88 and 133.97 (Aromatic methine), 150.67 (ArC-2), 163.73 and 169.50 (Ar$O\underline{C}$OMe and Ar$\underline{C}$(O)OR).

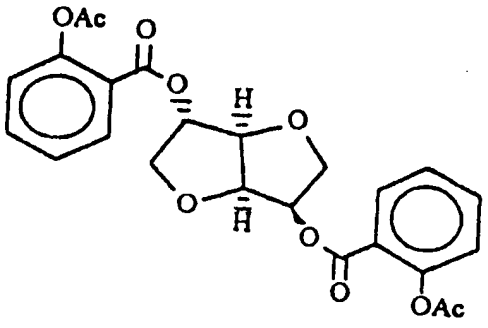
The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

APPENDIX 1

Isosorbide-2,5-Diaspirinate

Reaction Scheme:





CLAIMS

1. An isosorbide aspirinate compound.

2. Isosorbide – 2, 5 – diaspirinate.

3. Isosorbide – 2 – aspirinate.

4. Isosorbide – 5 – aspirinate.

5. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 4.

6. A pharmaceutical composition as claimed in claim 5 which is adapted for oral administration.

7. A pharmaceutical composition as claimed in claim 6 which is adapted for percutaneous administration.

8. A tablet or capsule including a compound as claimed in any of claims 1 to 4.

9. A transdermal patch including a compound as claimed in any of claims 1 to 4.

10. A suppository formulation including a compound as claimed in any of claims 1 to 4.

11. Use of a compound as claimed in any of claims 1 to 4 to achieve anti-platelet activity and/or other aspirin type activities such as anti-pyretic and/or anti-inflammatory activity.

12. A composition as claimed in any of claims 5 to 10 including another pharmaceutically acceptable entity.

13. A composition as claimed in claim 12 wherein the other pharmaceutically acceptable entity is a therapeutic oil.

14. A composition as claimed in claim 13 wherein the oil is a fish oil.

15. A composition as claimed in claim 14 wherein the oil is cod liver oil.

16. A composition as claimed in claim 13 wherein the oil is a vegetable oil.

17. A composition as claimed in claim 16 wherein the oil is evening primrose oil.

18. A composition as claimed in any of claims 12 to 17 wherein the composition is in the form of a capsule having a retaining shell containing a filling including the active ingredients.

19. A composition as claimed in claim 18 wherein the filling includes a suspending agent.

20. A composition as claimed in claim 19 wherein the suspending agent is selected from one or more of colloidal silicon dioxide, hydrogenated vegetable oils (optionally in combination with beeswax), and high melting point partial glycerides, and/or lecithins.

21. A composition as claimed in any of claims 18 to 20 wherein the filling includes an antioxidant.

22. A composition as claimed in claim 21 wherein the antioxidant is selected from one or more of D-alpha tocopherol, D-alpha tocopherol acetate, mixed tocopherols and ascorbic acid.

23. A composition as claimed in any of claims 18 to 22 wherein the shell is a gelatin shell.

24. A process for preparing a compound of claim 1 comprising reacting isosorbide with an acetylsalicyloyl in the presence of a base.

25. A process as claimed in claim 24 wherein the acetylsalicyloyl is acetylsalicyloyl chloride.

26. A process as claimed in claim 24 or 25 wherein the base is triethylamine.

27. A process as claimed in any of claims 24 to 26 wherein the reaction is carried out in a solvent.

28. A process as claimed in claim 27 wherein the solvent is toluene.

29. A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described with reference to the examples.

30. A compound substantially as hereinbefore described with reference to the accompanying examples.

31. A compound substantially as hereinbefore described with reference to the accompanying examples.

32. A use substantially as hereinbefore described with reference to the accompanying examples.

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/IE 97/00069

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H13/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 03421 A (CAL INT LTD ;BYRNE WILLIAM (IE); RYNNE ANDREW (IE)) 17 February 1994 see example 1 ---	1-32
A	WO 86 03206 A (OESTERR ZUCKERFAB EVIDENZ) 5 June 1986 see the whole document ---	1-32
A	DE 20 31 161 A (CIBA AG) 7 January 1971 see the whole document ---	1-32
P,X	WO 97 04757 A (CAL INT LTD ;BYRNE WILLIAM (IE); MCCAFFERTY DERMOT (IE)) 13 February 1997 see the whole document -----	1-32

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
6 February 1998	27. 02. 98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Steendijk, M

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[illegible]al Application No
PCT/IE 97/00069

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9403421 A	17-02-94	AU 1225795 A	04-05-95
		AU 673846 B	28-11-96
		AU 4581293 A	03-03-94
		CA 2141404 A	31-01-94
		CA 2141435 A	17-02-94
		EP 0656881 A	14-06-95
		EP 0676204 A	11-10-95
		GB 2284350 A,B	07-06-95
		GB 2284763 A,B	21-06-95
		IE 73463 B	04-06-97
		JP 7509484 T	19-10-95
		US 5665766 A	09-09-97
WO 8603206 A	05-06-86	AT 382624 A	25-03-87
		EP 0202305 A	26-11-86
DE 2031161 A	07-01-71	AT 333311 B	10-11-76
		BE 752862 A	04-01-71
		BG 19129 A	30-04-75
		CA 957682 A	12-11-74
		CH 539032 A	31-08-73
		DK 129985 B	09-12-74
		EG 11237 A	31-01-77
		FR 2059472 A	04-06-71
		GB 1317781 A	23-05-73
		LU 61240 A	10-09-70
		NL 7009806 A	05-01-71
		OA 3648 A	24-12-71
		SE 373849 B	17-02-75
		US 3781267 A	25-12-73
		ZA 7004274 A	31-03-71
WO 9704757 A	13-02-97	AU 6708996 A	26-02-97
		AU 6709096 A	26-02-97
		AU 6709196 A	26-02-97
		WO 9704758 A	13-02-97
		WO 9704759 A	13-02-97